

REMARKS

Claims 18, 28 and 31-91 are currently pending. Claims 32 and 34 have been canceled without prejudice. Claims 18, 28, 31, 45, 46, 48, 49, 74, 76, 77, 88 and 91 have been amended for purposes of clarity. Claims 35, 41, 50, 51, 58, 59, 76, 77, 86 and 87 have been amended so that they no longer depend on cancelled claims. Claims 59, 61, 63, 65, 67, 69, and 71 have been amended to comply with sequence rules requiring reference to an assigned sequence identifier, 37 CFR 1.821. New claims 92-99 mirror currently amended claims 76-77 and previously presented claims 78, 79, 80, 82, 83 and 84, respectively, and have been added to retain dependencies that were lost from claims 76 and 77 in the current amendments. The support for all claim amendments is found throughout the specification as filed. For example, support for the amendments to claims 18, 28, 31 and 88 may be found at page 9, lines 12-17; page 10, line 19 to page 11, line 3; page 27, lines 12 to 17 and page 44, line 6 to page 45, line 16. Support for the amendments to claims 45, 46, 48 and 49 may be found at page 38, lines 11 to 18. Support for the amendments to claims 76 and 77 may be found at page 9, lines 12 to 17; page 10, line 19 to page 11, line 3; and page 44, line 6 to page 45, line 9. Support for new claims 92 and 93 may be found at page 11, lines 1-2 and page 44, line 6 to page 45, line 4. Support for new claims 94-99 may be found at page 44, line 6 to page 45, line 4 and page 48, line 19 to page 49, line 2. No new matter has been introduced.

The Examiner has withdrawn claims 32 and 34 from further consideration under 37 C.F.R. § 1.142(b) as drawn to a non-elected invention. Thus, Applicants have cancelled claims 32 and 34 without prejudice. Applicants reserve the right to prosecute the subject matter of said claims in one or more related applications.

Objections to the Claims

The Examiner has objected to claims 35, 41, 50, 51, 58, 59, 72-77, 86-87 and 90-91 as reading on a non-elected invention. Claims directed to non-elected inventions have been cancelled, and Applicants have amended the remaining objected to claims to delete dependencies on cancelled claims. The objection is thus obviated.

The Examiner has objected to claims 59, 61, 63, 65, 67, 69 and 71 for failing to comply with sequence rule 37 C.F.R. § 1.821, in particular, for failing to reference the sequence HyXHyXHyXHy with an assigned identifier. In response, Applicants have amended these claims, as well as the specification at page 22, to identify the sequence with an appropriate sequence identifier. Additionally, Applicants submit herewith a Substitute Sequence Listing,

which includes the newly added sequence identifiers. Applicants have also requested hereinabove that the paper Substitute Sequence Listing submitted herewith be entered into the specification. The amendments and submission of a Substitute Sequence Listing obviate the objection.

The Rejections Under 35 U.S.C. § 112, Second Paragraph Should Be Withdrawn

The Examiner has rejected claims 18, 28, 31, 33 and 35-91 under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the invention. The Examiner contends that claims 18, 28, 31 and 88 are indefinite for failing to contain a conclusion that what was stated in the preamble was achieved. In response, Applicants have amended the independent claims 18, 28, 31 and 88, in part, to include a conclusion that the goal of the preamble was achieved, *i.e.* that an immune response was induced. The rejection is thus obviated

The Examiner has further rejected claims 18 and 31 under 35 U.S.C. § 112, second paragraph as allegedly indefinite because it is not clear what conditions are considered “physiologic.” Applicants respectfully disagree with the Examiner’s rejection. Applicants have defined physiologic conditions at page 26, line 19 to page 27, line 4 as

conditions of temperature, pH, ionic strength and molecular composition as are found within living organisms. For example, but not by way of limitation, physiological conditions would include temperatures of 4-55 °C, and preferably 20-40 °C; a pH of 3-12, and preferably 5-8; and ionic strengths of 50-300 mM NaCl, and preferably 100-200 mM NaCl.

In addition, Applicants have provided non-limiting examples of physiologic conditions, (see, *e.g.*, page 27, lines 4-7 and at page 21, line 18 to page 22, line 2). A patentee can be his own lexicographer. Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861, 228 U.S.P.Q. 90 (Fed. Cir. 1985). Thus, the definition and examples provided in the specification clearly convey to one of skill in the art the meaning of the term “physiologic” in the context of these claims. The rejection is thus overcome.

The Examiner has rejected claims 45, 46, 48 and 49 under 35 U.S.C. § 112, second paragraph as allegedly indefinite because “it is not clear what is implied by sensitive so as to allow the metes and bounds of the claim to be determined.” In response, Applicants have amended the claims to recite that said linkers are cleavable by acid, base, light, reduction, oxidation or a cellular enzyme. As understood in the art, “sensitive to cleavage by” and

“cleavable by” have the same meaning; thus, the amendment does not narrow the scope of the claims. The rejection is thus obviated.

The Examiner has rejected claim 74 under 35 U.S.C. § 112, second paragraph as indefinite because the phrase “substantially free of adjuvant” is allegedly unclear as compared to “not substantially free of adjuvant.” In response, Applicants have amended to the claim to delete “substantially,” thus obviating the rejection.

The Examiner has rejected claims 76 and 77 under 35 U.S.C. § 112, second paragraph as indefinite as it is allegedly unclear when an antigen is considered to be associated with a pathogen or with a neoplasia, respectively. In response, by way of clarification without changing the scope of the claims, Applicants have amended the claims to recite that the immune response is induced to an antigen of said pathogen or said neoplasia, respectively, thus obviating the rejection.

The Examiner has rejected claim 91 under 35 U.S.C. § 112, second paragraph as indefinite as allegedly the terms “... analog and derivate carry no weight in terms of structure and function and encompasses [sic] an unlimited number of alterations and reads [sic] on unrelated molecules.” In response, Applicants have amended the claim to delete “analog.” Applicants submit that the term “derivative,” however, is well understood in the art. Words in the claims are generally given their ordinary and customary meaning, as understood by one of ordinary skill in the art at the time of the invention. See Phillips v. AWH Corp., 415 F.3d 1303, 1312-13; Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996). Benzoquinone ansamycin antibiotics are not novel compounds and the literature is rife with teachings of characteristics of both the compounds themselves and their derivatives. As such, one of skill in the art could readily ascertain the meaning of the term “derivative” in the context of these claims. Moreover, extrinsic evidence, such as dictionaries, can assist in determining the meaning of particular terminology to those of skill in the art of the invention. See Phillips, 415 F.3d at 1318, citing Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 325 (Fed Cir. 2002). The attention of the Examiner is invited to Exhibit A, attached hereto, which is a copy of page 384 of The American Heritage Dictionary (2nd Ed., 1982, Houghton Mifflin Co.), presenting the definition of “derivative.” As set forth in definition 4 of Exhibit A, a derivative is “[a] compound derived or obtained from known or hypothetical substances and containing essential elements of the parent substance.” It would thus be clear to one skilled in the art that a derivative of a benzoquinone ansamycin antibiotic contains essential elements of the structure

of the parent antibiotic sufficient to make the derivative recognizable as a compound derived from the parent compound. Thus, the rejection should be withdrawn.

The Examiner has rejected claims 33, 35-44, 47, 50-73, 75 and 78-90 for depending on an indefinite base claim. For the reasons discussed above, the base claims are not indefinite, and the rejection of these claims is thus obviated.

Accordingly, in view of the foregoing, the rejections under 35 U.S.C. § 112, second paragraph, have been overcome or obviated and should be withdrawn.

The Rejections Under 35 U.S.C. § 112, First Paragraph, For Lack Of Enablement, Should Be Withdrawn

The Examiner has rejected claims 18, 28, 31, 33 and 35-91 under 35 U.S.C. §112, first paragraph, because allegedly the specification does not enable one of skill in the art to use a conjugate peptide comprising a heat shock protein binding portion and an antigenic portion, other than the OVA-BiP peptide construct disclosed in the specification, to induce an immune response against the antigen. Applicants respectfully disagree.

In particular, the Examiner contends that “a conjugate peptide comprising the hsp70 plus OVA-BiP peptide construct disclosed in the specification does not reasonably provide enablement for the use of other constructs.” (see page 6 of the Office Action, lines 3-6). The Examiner repeats essentially the same contention later on page 6, second paragraph, lines 6-12, and adds that “[t]here is no disclosure in the specification regarding provoking an immune response using conjugates isolated from gp96.” (see page 6 of the Office Action, second paragraph, lines 5-7). Applicants point out that under the applicable case law, it is improper to limit Applicants to the specific example presented, notwithstanding the disclosure and enablement of a broader invention. See In re Anderson, 176 U.S.P.Q. 331, 333 (C.C.P.A. 1973); In re Kamal, 158 U.S.P.Q. 320, 323 (C.C.P.A. 1968).

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. U.S. v. Telectronics Inc., 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). In fact, well known subject matter is preferably omitted. See Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986) (“a patent need not teach, and preferably omits, what is well known in the art.”). One skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. See Northern Telecom, Inc. v. Datapoint Corp., 908 F.2d

931, 941 (Fed. Cir. 1990) (“A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation.”). These enablement rules preclude the need for the patent applicant to “set forth every minute detail regarding the invention.” Phillips Petroleum Co. v. United States Steel Corp., 673 F. Supp. 1278, 1291 (D. Del. 1991); see also DeGeorge v. Bernier, 768 F.2d 1318, 1323 (Fed. Cir. 1985).

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. Fields v. Conover, 170 USPQ 276, 279 (CCPA 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

Applicants respectfully point out that enabling support for the claimed methods is provided throughout the specification in form of guidance on how to identify a tether that binds to a heat shock protein, how to make the conjugate comprising a protein tether as well as a non-protein tether, and how to use the conjugate to obtain an immune response. In particular, Applicants direct the Examiner’s attention to the lengthy list of heat shock protein binding tethers on pages 29 to 37 of the specification, the detailed method of identifying peptide hsp-binding tethers at page 17, line 2 to page 19, line 13 and to the working examples of methods to identify such tethers using heat shock protein gp96 in Example 6, at page 49, line 14 to page 70, line 37. Applicants additionally disclose non-peptide based hsp tethers, in particular benzoquinone ansamycin antibiotics (see the specification at pages 37-38), and their use in the manufacture of the conjugate peptide of the invention at page 38, line 19 to page 42, line 16. Methods for production of conjugate peptides comprising peptide tethers, *e.g.* chemical synthesis or using recombinant techniques (see the specification page 45, lines 11-15) are well known in the art. Similarly, immunization procedures for an immunogen of interest were well known in the art at the time the application was filed. Given the detailed teachings in the specification as described above, the amount of literature referred to in the specification, and the high level of skill in the art, the experimentation to make and use the claimed methods throughout their scope is routine and thus, the full scope of the claimed methods is enabled.

As further evidence of the enabling nature of the disclosure, Applicants submit herewith as Exhibit B the Declaration of Dr. Brian H. Barber, which was submitted under 37 C.F.R. § 1.132 in connection with the prosecution of U.S. Serial No. 09/680,806, now U.S. Patent No. 6,719,974, and which shows the positive induction of an immune response in test animals using the claimed methods of the instant application. In paragraph 7 at page 5 of the Declaration, Dr. Barber explains the relevant study. Test mice were immunized twice over seven days with test compounds and subsequently challenged by inoculation of tumor cells expressing the antigen ovalbumin (OVA). Figure 3 on page 5 of the Declaration shows that administration of a conjugate peptide comprising the antigenic domain of OVA, SIINFEKL, the heat shock protein binding domain NLLRLTGW, and a FFRL linker (closed squares), in the absence of heat shock protein or other adjuvants, was able to induce tumor protection. The induction of tumor protection indicates that a protective immune response was achieved.

The Examiner further alleges that the tether that binds to the heat shock protein is not defined by structure, and in particular, that the specification does not disclose a critical feature defining what sequence of polypeptide will bind to heat shock proteins and be effective to provoke an immune response (see Office Action page 6, line 20 to page 7, line 1. Applicants disagree and point out that a consensus sequences have been provided at page 28, lines 7-9. In addition amino acid amino acid preferences and 164 exemplary tethers which satisfy the consensus sequence are provided at page 27, line 19 to page 37, line 13. Example 6 also presents numerous methods for identification of tethers under altered binding conditions along with a discussion of the structural changes in the identified tethers effected by the change in binding conditions, *e.g.*, page 57, lines 1 to 11. Applicants also point to Srivastava 2002: *Ann. Rev. Immunol.* 20:395-425 (Ref. C29 of record in the Supplemental Information Disclosure Statement submitted herewith), which points out the extreme promiscuity with which heat shock proteins bind peptides, consistent with their “primordial” role in the folding and assembly of proteins (see Srivastava, page 402, first full paragraph). This shows that heat shock protein binding peptides are ubiquitous and thus only routine experimentation is expected in order to obtain an heat shock protein-binding peptide by screening. Given the detailed teachings, working examples and level of skill in the art, identification of yet other tethers in accordance with the invention would be routine.

The Examiner alleges that the scope of the claim encompasses all constructs which may be incapable of inducing an immune response under a wide variety of binding conditions, and refers to the unpredictability of immuno-modulation. However, the Examiner has not come forward with any specific evidence to substantiate his speculative assertion that some constructs may not induce an immune response. The Patent and Trademark Office bears the initial burden

of establishing a *prima facie* case of non-enablement. *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A. 1971); MPEP § 2164.02. A patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless there is reason to doubt the objective truth of the teachings which must be relied on for enabling support. *Id.* Applicants point out that it is established in the art and taught in the specification that heat shock proteins bind a wide variety of different peptides under physiologic conditions (see *e.g.*, Ref. C29) and play a significant role in the stimulation of an immune response, *e.g.*, as an adjuvant (see page 6, line 19 to page 3). It is also well known that complexes of heat shock protein and an antigen are involved in antigen presentation resulting in the induction of an immune response specifically against the antigen that is bound to the heat shock protein in the complexes (see WO 97/06685 corresponding to PCT/US96/13233, reference of record in the Information Disclosure Statement submitted on May 9, 2003). Applicants have provided working examples demonstrating the induction of an immune response using the exemplary conjugate peptides of the invention. Applicants submit that only routine experimentation by a skilled person is required to practice the claimed invention. If the Examiner is relying on any other facts within his personal knowledge as to why the methods of the invention would not be effective in inducing an immune response he is hereby requested to supply an affidavit specifying with particularity the support for the rejection. 37 C.F.R. § 1.104(d)(2).

In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

The Rejections Under 35 U.S.C. § 112, First Paragraph, For Lack Of Written Description, Should Be Withdrawn

The Examiner has rejected claims 18, 28, 31, 33 and 35-91 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. In particular, the Examiner states that

The instant disclosure of an hsp70/ova-BiP construct that can induce an immune response does not adequately describe the scope of the claimed genus, which encompass a substantial variety of subgenera including constructs which encompass proteins/non-proteins which bind "heat shock protein".....[t]he tether that binds the heat shock protein is not defined by structure.

Applicants respectfully disagree and assert that the specification as filed provides an adequate written description for the claimed methods comprising a conjugate peptide. An adequate written description of the conjugate peptides does not require that the specification

provide a detailed structure of every, or even most, species of the conjugate peptides, for the reasons set forth below.

The legal standard for the written description requirement of 35 U.S.C. § 112, first paragraph, requires that an applicant “must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.” Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555; 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). According to the relevant case law, a claimed genus may be supported by a representative number of species or a description of structural features common to members of the genus. Regents of University of Ca. v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997), cert. denied 523 U.S. 1089 (1998). What constitutes a “representative number of species” depends upon the knowledge and skill in the art. Moreover, such a description need not be sufficient to provide support to claim each individual species encompassed by the genus. The description is deemed sufficient if it demonstrates to the skilled artisan that the applicant was in possession of the necessary common attributes of the members of the genus. *Eli Lilly*, 119 F.3d at 1568.

The Examiner’s attention is directed to the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶ 1, “Written Description” Requirement” (“the Guidelines”) (published in the January 5, 2001 Federal Register at Volume 66, Number 4, pages 1099-1111). The Guidelines specify that an applicant may show that an invention is complete by “disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention.” (*Id.* at page 1106, column 1, lines 22-33). According to the Guidelines, for each claimed genus, the test requires determination of whether there is sufficient description of

. . . a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus.

Id. at page 1106, col. 3, lines 12-29

According to the Guidelines, there are situations where description of even one species adequately supports a genus. “Satisfactory disclosure of a “representative number” depends on whether one of skill in the art would recognize that the applicant was in

possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.” (*Id.* at page 1106, col. 3, lines 42-50). Where the specification discloses any relevant identifying characteristics, *i.e.*, physical, chemical and/or functional characteristics, sufficient to allow a skilled artisan to recognize the applicant was in possession of the claimed invention, a rejection for lack of written description under Section 112, first paragraph, is misplaced.

The instant claims are directed to methods of inducing an immune response comprising administering a composition comprising a conjugate peptide. The conjugate peptide comprises a portion which binds to a heat shock protein (the tether) and a portion which is antigenic. The tether may be a peptide or a non-peptide, *e.g.* a benzoquinone ansamycin antibiotic.

The case law on which the Examiner based his rejection discussed written description requirements in the context of claiming nucleic acids. In particular, the Examiner relied on The Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998), wherein the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. Applicant respectfully points out that this holding regarding a genus of nucleic acids is not applicable to the instantly claimed invention, as discussed below. *Eli Lilly* concerns claims directed to genera of vertebrate and mammalian insulin cDNAs based merely on the disclosure of a single species, rat insulin cDNA, a prophetic method for obtaining another species (human insulin cDNA), and the functional activity of the other species in the claimed genera. *Id.* The court in *Eli Lilly* held that a “description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, . . . or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus” [footnote omitted]. *Id.* at 1569.

The Examiner further relies on Fiers v. Revel, 984 F.2d 1164, 1170 (Fed. Cir. 1993). The principle set forth in Fiers is that the description of a method of isolating a cDNA does not provide a written description of that cDNA. In Fiers, the Applicants’ description of a method of isolating a human fibroblast β interferon DNA was asserted to have provided a written description of the DNA itself.

An adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it; what is required is a description of the DNA itself. . . [such as] by

structure, formula, chemical name, or physical properties.”) Fiers v. Revel, 984 F.2d 1164, 1170 (Fed. Cir. 1993)

The instant application is clearly distinguishable from that in either Eli Lilly or Fiers in that the specification provides the amino acid sequences of over 160 representative peptide tethers (see the specification at pages 29 to 37) as well as representative non-peptide tethers (see the specification at page 37, line 15 to page 38, line 6), provides the structural features common to the members of the genus of tethers in the form of a consensus sequence (see specification at page 28, lines 7-9), and describes that a method of identifying tethers has been successfully performed (Section 5.1, page 15 and Example 6, page 49).

The conjugate peptides of the instant application have in common the characteristic of comprising a tether which associates with a heat shock protein. Because heat shock proteins are not limited in binding to a particular structure of peptide (see, e.g. Ref. C29 cited above), the claims encompass peptides that are, in contrast to the nucleic acids of the claims at issue in Eli Lilly or Fiers, diverse in nature and lack any common structural features other than containing a majority of hydrophobic residues or the hydrophobic consensus sequence as set forth in the specification at page 27, line 19 to page 28, line 7. Thus, the application has provided a common structural feature that gives rise to a written description of the genus, as well as the identifying characteristic of binding to heat shock protein.

The instant specification thus provides both a consensus sequence and over 160 examples of suitable tethers (page 27, line 19 to 37 and page 37 line 15 to page 38, line 6). Given the consensus sequence of the tether (page 28, lines 7-9), and the teaching of particular tethers in the specification, Applicants submit that the specification provides an adequate written description of the conjugate peptide of the claimed methods given the appropriate standard elucidated above.

In view of the foregoing, Applicants respectfully request that the rejections under 35 U.S.C. §112, first paragraph be withdrawn.

CONCLUSION

Applicants respectfully request that the amendment and remarks made herein be entered and made of record in the instant application. If any issues remain in connection

herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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Exhibit A

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1930's. [After the Great Depression, a period of severe economic hardship during the 1930's.] *adj.* 1. Causing depression. 2. Of or pertaining to psychological depression. —*de-pres'ərively adv.* —*de-pres'əriveness n.*

de-pres'or (di-prē'sər) *n.* 1. Something that depresses or is used to depress. 2. A depressor nerve. 3. Any of several muscles that cause depression or contraction of a part. 4. An instrument used to depress a part.

depressor, nerv. *n.* A nerve that lowers arterial blood pressure.

de-pres'urize (di-prēsh'ə-riz') *tr. v.* —*iz·ed, -ir·ing, -ize·s·* To release from pressure. —*de-pres'uriza·tion n.*

depriv·al (di-prī'vəl) *n.* Deprivation.

depriv·a·tion (dē-prīvā'shən) *n.* 1. a. The act of depriving; loss. b. The condition of being deprived; privation. 2. A removal of rank or office.

de-prive (di-prīv') *tr. v.* —*priv·ed, -priv·ing, -priv·es.* 1. To take something away from; dispossess: Redistricting deprived the state of two congressional seats. 2. To keep from possessing or enjoying; deny: He was deprived of his just acclaim. 3. To remove from office. [ME *depriven* < OFr. *deprivē* < Med. Lat. *deprivare* *Lat.* *de-*, completely + *Lat. privare*, to rob, *privus*, without] —*depriv·er adj.*

de-prived (di-prīvd') *adj.* Characterized by deprivation, esp. of economic or social necessities.

de-pro·gram (di-prō grām', -grām') *tr. v.* —*grammed, -gram·ming, -gram·ed, -gram·ing, -grams.* To counteract or try to counteract the effect of an indoctrination, esp. a religious indoctrination. —*de-pro·gram'mer n.*

depth (dēpth) *n.* 1. The condition or quality of being deep. 2. a. The extent, measurement, or dimension, downward, backward, or inward. b. The linear measurement or sense of distance from an observation point, especially in painting. 3. Often depths. A deep part of or place: *in the depths of the forest*. 4. The most profound or intense part or stage: *the depth of despair*. 5. The severest or worst part: *in the depth of winter*. 6. A bad or deteriorated condition: *Productivity has fallen to incredible depths*. 7. Intellectual complexity or penetration; profundity: *a novel of great depth*. 8. The range of one's understanding or competence: *beyond one's depth*. 9. The degree of richness or intensity: *depth of color*. 10. Lowness in pitch: *Idiots in depth*. With thoroughness: *a study in depth*. [ME *deþe* < *dēp*, *deep*.]

depth charge *n.* A charge designed for explosion under water, used esp. against submarines.

depth perception *n.* Perception of spatial relationships, esp. of distances between objects, in three dimensions.

depth psychology *n.* 1. Psychology of the unconscious, esp. as distinguished from the psychology of conscious behavior. 2. Psychoanalysis.

de·pur·ate (dē-pür'ət) *tr. & intr. v.* —*rat·ed, -rat·ing, -rates.* To clean or purify or become cleansed or purified. [ME *depurare* < L Lat. *depurare*, *depur-* *Lat. de-*, away + *purus*, pure.] —*de·pur·a·tion n.* —*de·pur·a·tor n.*

deput·a·tion (dē-pütā'shən) *n.* 1. a. The act of deputing. b. The state of being deputed. 2. A person, or group, appointed to represent another or others; delegation.

de·put·e (dē-pü'tē) *tr. v.* —*put·ed, -put·ing, -put·es.* 1. To appoint or authorize as an agent or representative. 2. To assign (authority or duties) to another; delegate. [ME *deputē* < OFr. *deputē* < L Lat. *depurare*, to allot < Lat., to consider, *de-*, apart, away + *putare*, to trim, arrange.]

deput·ize (dē-püt'ēz) *tr. & intr. v.* —*rat·ed, -rat·ing, -rates.* To appoint as or serve as a deputy. —*de·put·i·za·tion n.*

deput·y (dē-pü'tē) *n.* *pl.* *dees.* 1. A person named or empowered to act for another. 2. An assistant exercising authority in the absence of his superior and equal authority in emergencies. 3. A representative in a legislative body, certain countries. [ME *depute* < OFr. *deputé*, *de-*, part of *deputer*, to appoint.]

de-rac·i·nate (dē-rā'shə-nāt') *tr. v.* —*nated, -nating, -na·tions.* To pull out by or as if by the roots; uproot. [Fr. *déraciner*, OFr. *desraciner*, *des-*, apart (< Lat. *dis*) + *racine*, root. LLat. *radicina* < Lat. *radix*] —*de·rac·i·na·tion n.*

de-rail (dē-räl') *intr. & tr. v.* —*railed, -rai·ling, -rai·ls.* 1. To run or cause to run off the rails. 2. To be thrown or thrown off course. [Fr. *dérailier*, *de-*, off (< Lat. *de*), + *rai*, rail, rail < L Lat. *radix*, root] —*de·rai·lal n.*

de-rail·leur (di-räl'yar) *n.* A gear mechanism on a bicycle that changes, bicycle gear ratio by moving the chain from one sprocket to another. [Fr. *dérailleur*, to become derailed + *de-*, off (< Lat. *de*) + *rai*, rail < L Lat. *radix*, root]

de-range (di-rānj') *tr. v.* —*range·ed, -range·ing, -range·as.* 1. To disturb: *To disturb the normal condition or functioning of.* 2. To make insane. [Fr. *deranger* < OFr. *desriger*, *des-*, apart (< Lat. *dis*) + *re-*, line, of Germanic orig.] —*de·range·ment n.*

de-ral·ly (dē-räl'ē) *n.* *pl.* *de·ras.* 1. Any of various annual horse races; esp. for three-year-olds. 2. A horse race with a more or less open field of contestants: a motor cycle derby. 3. A stiff felt hat with a round crown and narrow, curved brim. [After Edward Smith Stanier (1752-1834), 12th Earl of Derby, founder of the English Derby.]

de-reg-ū-lātē (dē-rēg'yo-lātē) *n.* -lated, -lat-ing, -lates. To decontrol. —de-reg-u-la-tion (dē-rēg'yo-lāshən) *n.* The act of deregulating.
de-re-lict (dē-rē-likt') *adj.* 1. Neglectful of duty or obligation; remiss. 2. Deserted by an owner or guardian; abandoned. —*n.* 1. Abandoned property; esp., a ship abandoned at sea. 2. A homeless or jobless person; vagrant. 3. *Law.* Land left dry by a permanent recession of the water line. [*Lat.* *dērelictus*; *pi* part. of *dērelinquer* 'to abandon' + *linquere*, to leave].
de-reli-cion (dē-rē-lik'shən) *n.* 1. Willful neglect of duty. 2. Abandonment. 3. *Law.* A gaining of land by the permanent recession of the water line. **b.** The land so gained.
de-rid-e (dē-rid') *v.* -rid-ed, -rid-ing, -rid-es. To speak of or treat with contemptuous mirth; [*Lat.* *deridere*, *de-* (pejorative) + *ridere*, to laugh at]. —*de-rid'er n.* —de-rid-ing'ly *adv.*
de-ri-gue (dē-rē-gyoo') *adj.* Required by the current fashion or custom; socially obligatory. [*Fr.*]
de-ri-tion (dī-rīsh'ən) *n.* 1. *a.* An act of deriding; ridicule. **b.** A state of being derided. 2. An object of ridicule; laughingstock. [*ME derisoun* < *OFr.* *derision* *Lat.* *derisio* < *Lat.* *derisus* p. part. of *deridere*, to deride].
de-ri-sive (dē-rē'siv) *n.* **a.** *1.* *a.* Mocking, scoffing. **b.** *2.* *a.* *derisively* *adv.* *2.* *a.* Derivative.
de-ri-vate (dē-rē'vet) *adj.* *1.* *a.* Resulting from derivation. **b.** Copied or adapted from others: a *derivative prose style*. **c.** *1.* Something derived. **2.** *ling.* A word formed from another by derivation. **3.** *Math.* The limit, as the increment in the argument of a function approaches zero, of the ratio of the increment in its value to the corresponding increment in the argument; the instantaneous rate of change of a function with respect to a variable. **4.** *Chem.* A compound derived or obtained from known or hypothetical substances and containing essential elements of the parent substance. **5.** *math.* *derivative* *adv.* *6.* *math.* *derivative-ness n.*
de-ri-vative (dē-rē'vetiv) *adj.* *1.* Resulting from derivation. *2.* Copied or adapted from others: a *derivative prose style*. *3.* *ling.* A word formed from another by derivation. *4.* *math.* The limit, as the increment in the argument of a function approaches zero, of the ratio of the increment in its value to the corresponding increment in the argument; the instantaneous rate of change of a function with respect to a variable. *5.* *chem.* A compound derived or obtained from known or hypothetical substances and containing essential elements of the parent substance. *6.* *math.* *derivative* *adv.* *7.* *math.* *derivative-ness n.*
de-ri-vat-ive (dē-rē'vetiv) *n.* *1.* *1.* To obtain or receive from a source. *2.* To arrive at by reasoning, deduce or infer; *derive a conclusion from facts*. *3.* To trace the origin or development of (a word, for example). *4.* *chem.* To produce or obtain (a compound) from another substance by chemical reaction. —*int.* To issue from a source; originate. [*ME derive*, to be derived from < *OFr.* *deriver* *Lat.* *deri-vare*, to derive; *de-* away + *ri-va*, stream]. —*de-ri-vat-ive adj.* —*de-ri-vat-ive n.*
derm (dērm) *n.* Variant of *derma*.
derm- *pref.* Variant of *derma*.
—derm suff. Skin; covering. *blastoderm* < *Gk.* *dermī*, skin.
derm'a (dēr'mā) also *derm* (dērm) or *dermis* (dēr'mīs) *n.* *Anat.* The corium. [*Lat.* *derm* < *Gk.* *skin*].
derm'a (dēr'mā) *n.* Beef casing stuffed with a seasoned mixture of matzo meal or flour, onion, and suet, prepared by boiling, then roasting. [*Yiddish* *derme*, pl. of *derm*, intestine. < *MHG* < *OHG*].
derm- or *derm-* *pref.* Skin; *dermal* [*Gk.* *derma*, skin].
—derma suff. Skin, skin disease. *sceroderma* [*NLat.* < *Gk.* *derma*, skin].
der-ma-brasion (dēr'mā-brāzhōn) *n.* A surgical procedure designed to remove skin imperfections, such as scars or wrinkles, through the abrasion of the frozen epidermis.
der-mal (dēr'māl) also *derm-ic* (mīk) *adj.* Of or pertaining to the skin.
dermat- *pref.* Variant of *dermato-*.
dermat-itis (dēr'mā-tīt's) *n.* Inflammation of the skin.
dermat- or *dermat-* *pref.* Skin: *dermatome* [*Gk.* *derma*, skin].
dermat-ogen (dēr'mātō-jān) *n.* *Bot.* The outer layer of meristematic tissue, from which the epidermis is formed.
dermat-oid (dēr'mā-toid') *n.* Resembling skin.
dermat-ology (dēr'mā-tōl'ōjē) *n.* The medical study of the physiology and pathology of the skin. —*dermat-olog* (dēr'mā-tōl'ōjik) *adj.* —*dermat-olog-ist* (dēr'mā-tōl'ōjist) *n.*
dermat-ome (dēr'mā-tōm) *n.* The lateral wall of a somite from which the corium is formed.
dermat-o-phyte (dēr'mātō-fīt', dēr'mā-tōz) *n.* Any of various fungi that cause skin disease. —*dermat-o-phytic* (fīt'ik) *adj.*
dermat-ophy-to-sis (dēr'mātō-fītō'sis) *n.* Athlete's foot.
dermat-o-plas-ty (dēr'mā-tō-plas'tē) *n.* The use of skin grafts in plastic surgery, to correct defects or replace skin loss.
dermat-otrans-plant (dēr'mā-tō-trān'splānt) *n.* A skin graft taken from another person.



darby

Exhibit B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	09/680,806	Confirmation No. 2427
Applicant	:	Rothman et al.	
Filed	:	October 5, 2000	
TC/A.U.	:	1642	
Examiner	:	Minh-Tam B. Davis	
Docket No.	:	11746/46104	
Customer No.	:	26646	

Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**DECLARATION UNDER 37 C.F.R. § 1.132 OF
DR. BRIAN H. BARBER**

I, Brian H. Barber, Ph.D., do hereby declare as follows:

1. I currently hold the position of Senior Vice President and Chief Scientific Officer at Mojave Therapeutics, Inc., 22 Saw Mill River Road, Hawthorne, New York 10532
2. My background is in cellular immunology. My professional experience is further detailed in my *curriculum vitae*, which is attached hereto as **Exhibit A**.
3. Mojave Therapeutics, Inc. is the exclusive, worldwide licensee of the above-referenced patent application from Memorial Sloan-Kettering Cancer Center.

4. I have carried out various studies directed at evaluating the range of heat shock protein binding domains useful in the hybrid antigens of the above-referenced patent application. The following table summarizes the data that is described in further detail below.

Table 1

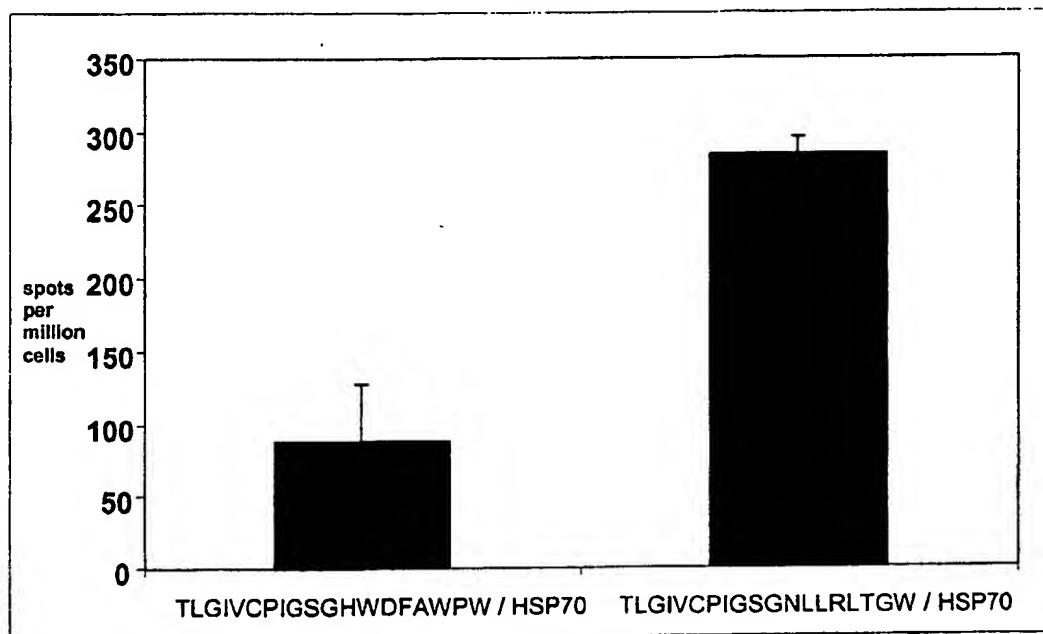
Heat shock protein binding domain sequence	Antigenic domain sequence (Class I MHC)	Cellular Immune Response (paragraph #)	Clinical Result (paragraph #)
HWDFAWPW and NLLRLTGW	TLGIVCPI (human HLA-A2)	(5)	
HWDFAWPW	IMDQVPFSV and YMDGTMSQV (human HLA-A2)	(6)	
NLLRLTGW	SIINFEKL (mouse H2-K ^b)		Mouse: lymphoma (7)
NLLRLTGW	IMDQVPFSV (human HLA-A2)	(8)	
NLLRLTGW	YMDGTMSQV (human HLA-A2)	(9)	
NLLRLTGW	SVYDFFVWL (both mouse H2-K ^b and human HLA-A2)		Mouse: melanoma broke tolerance (10)
FYQLALTW and RKLFFNLRW	SIINFEKL (mouse H2-K ^b)	(12)	

Detailed description of support for data in Table 1:

5. Non-covalent complexes of recombinant human heat shock protein 70 and hybrid antigens of the invention comprising an HLA-A2 epitope from human papillomavirus E7 protein (TLGIVCPI, amino acids 86-93), and either the heat shock protein binding domain HWDFAWPW or NLLRLTGW, were evaluated for biological activity *in vivo* in HHDII transgenic mice that express an HLA-A2 haplotype (Firat et al., 1999, *Eur. J. Immunol.* 1999

Oct; 29(10):3112-21). To evaluate the induction of an antigen-specific immune response in this model that is predictive of an expected response in humans, mice were immunized on day 0; on day 7, splenocytes were obtained from the immunized animals and were restimulated with peptide (TLGIVCPI) alone *in vitro* for 5 days, after which the percent of γ -interferon-secreting CD8+ cells was determined by ELISPOT. The results are shown in Figure 1, below.

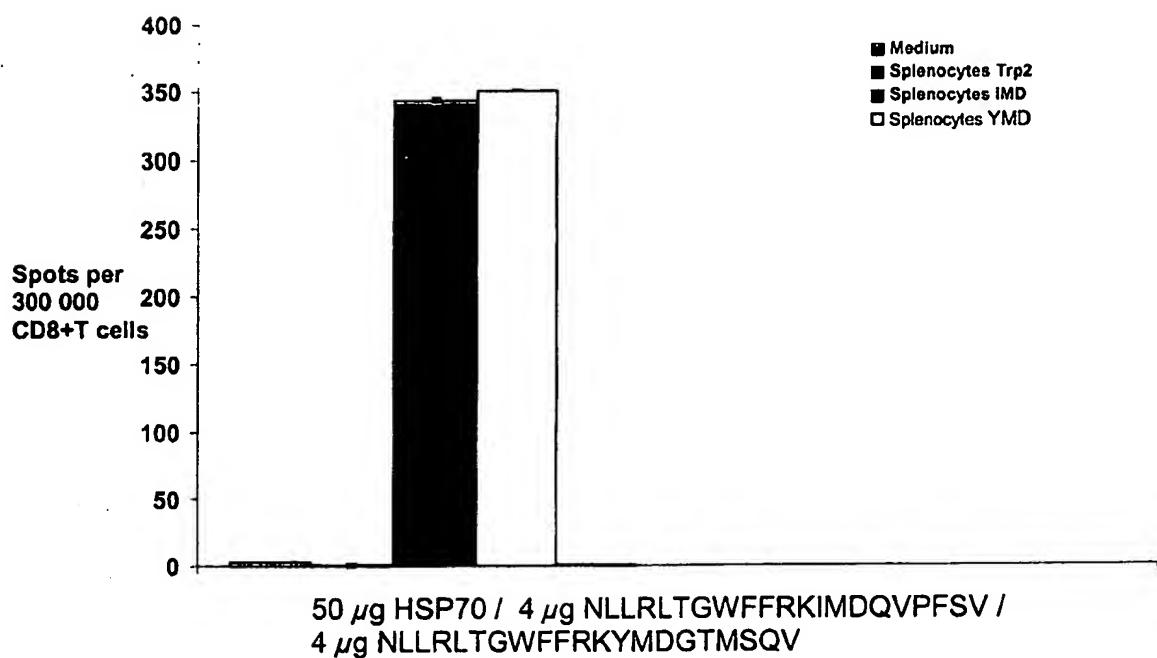
Figure 1



6. Non-covalent complexes of recombinant human heat shock protein 70 and hybrid antigens of the invention containing either of two human HLA-A2 melanoma epitopes were evaluated for biological activity *in vivo* in HHDII transgenic mice that express an HLA-A2 haplotype (Firat et al., 1999, *Eur. J. Immunol.* 1999 Oct; 29(10):3112-21). To evaluate the induction of an antigen-specific immune response in this model that is predictive of an expected

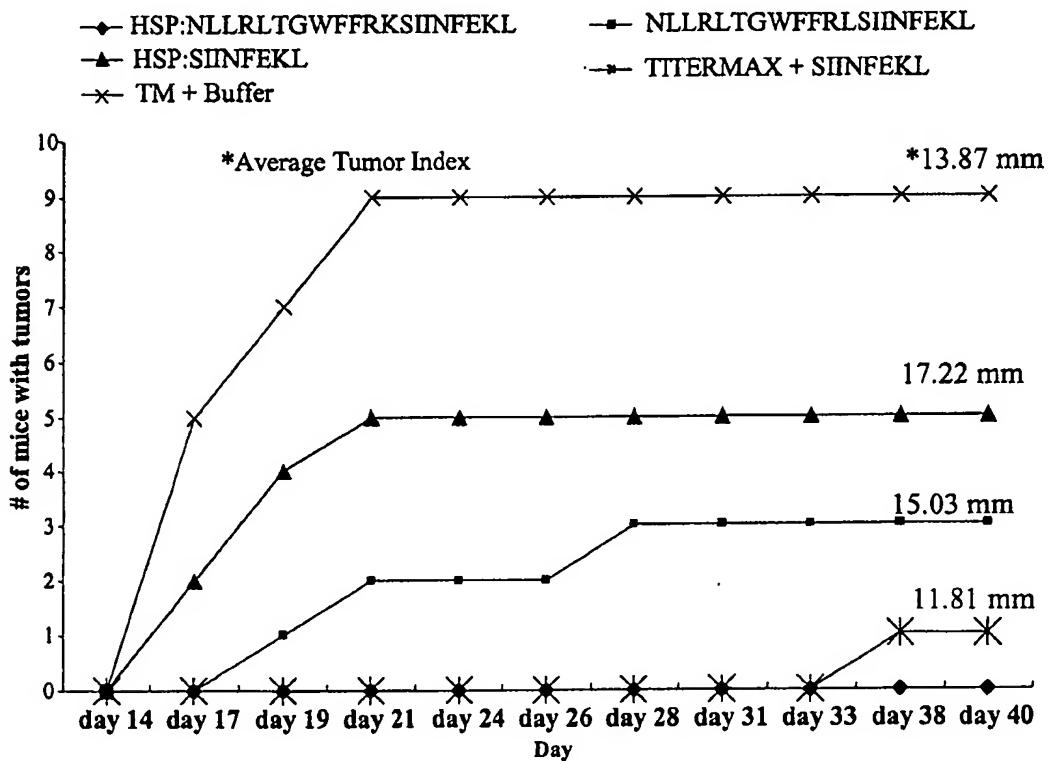
response in humans, mice were immunized on day 0 with both complexes; on day 7, splenocytes were obtained from the immunized animals and were restimulated with peptide alone (IMDQVPFSV or YMDGTMSQV) *in vitro* for 5 days, after which the percent of γ -interferon-secreting CD8+ cells was determined by ELISPOT. The results are shown in Figure 2, below, and demonstrate simultaneous responses to both antigens.

Figure 2



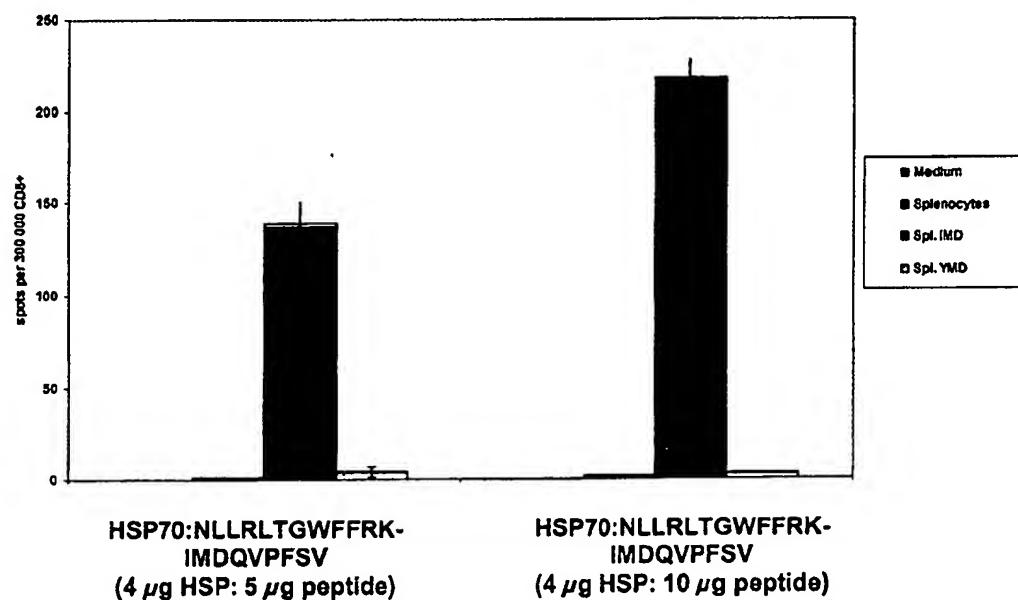
7. In tumor-killing studies similar to that described in Moroi et al., *ibid.*, B6 mice (10 animals per group) were immunized with complexes of the invention or controls on days 0 and 7, and then challenged on day 16 by subcutaneous injection of 10^5 E.G7 lymphoma cells that were engineered to express ovalbumin, and by presenting the epitope SIINFEKL (OVA) are targets for killing by OVA-specific CTLs. Figure 3 below shows the results after 40 days. Average tumor size is indicated by each group.

Figure 3



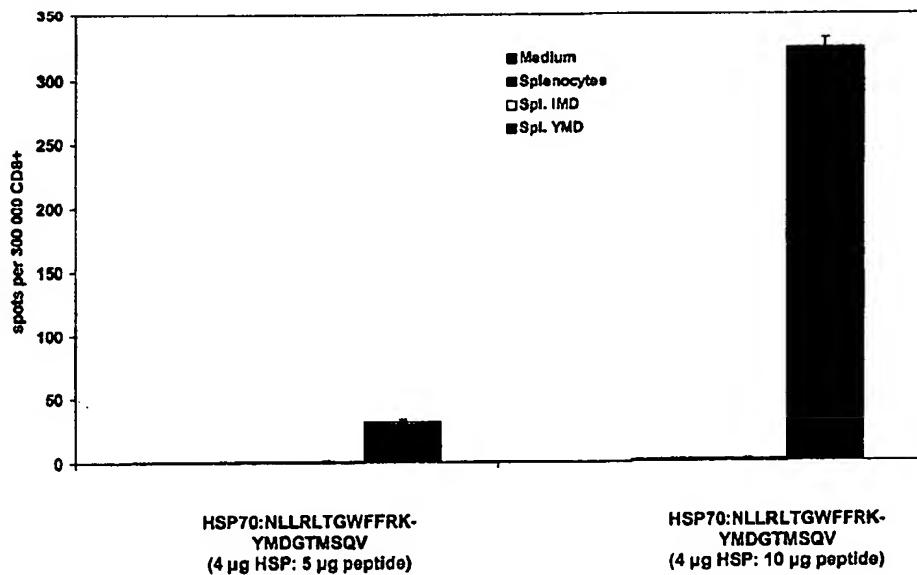
8. Studies in HHDII mice with complexes containing the gp100 melanoma HLA-A2 epitope were performed in the same manner as paragraph 5 above. Two dose levels were evaluated as shown in Figure 4, below. The CD8+ T cell responses were specific for the gp100 epitope.

Figure 4



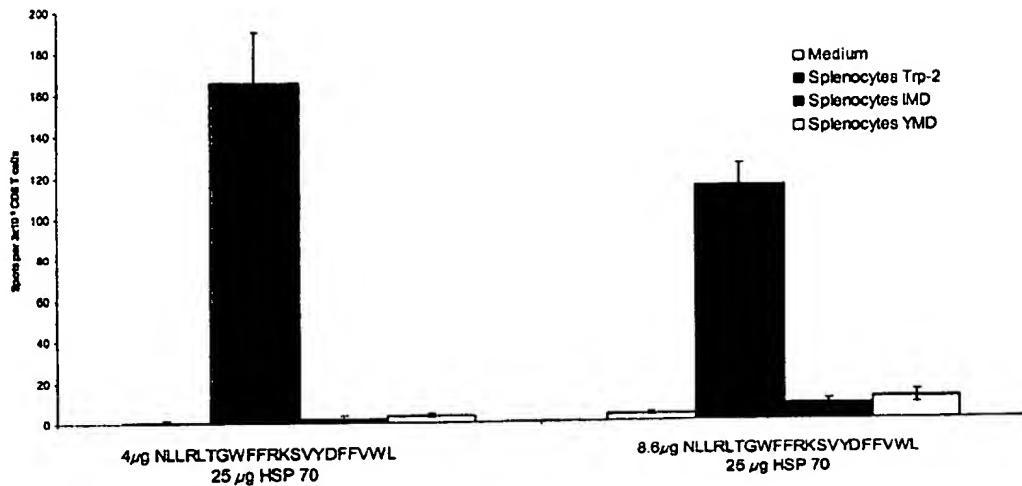
9. Studies in HHDII mice with complexes containing the tyrosinase melanoma HLA-A2 epitope were performed in the same manner as the study above. Two dose levels were evaluated, as shown in Figure 5, below. The CD8+ T cell responses were specific for the tyrosinase epitope.

Figure 5



10. The epitope SVYDFFVWL, amino acids 180-188 from the melanoma-associated antigen trp-2 is both a human HLA-A2 Class I epitope and a murine H2-K^b Class I epitope. Because HHDII transgenic mice express a human HLA-A2 Class I haplotype on a B6 mouse background, this epitope represents a "self" epitope for which an immune response generated in the HHDII model is indicative of breaking tolerance in humans. The results of an *in vivo* experiment performed in a similar fashion to those described above is shown in Figure 6.

Figure 6

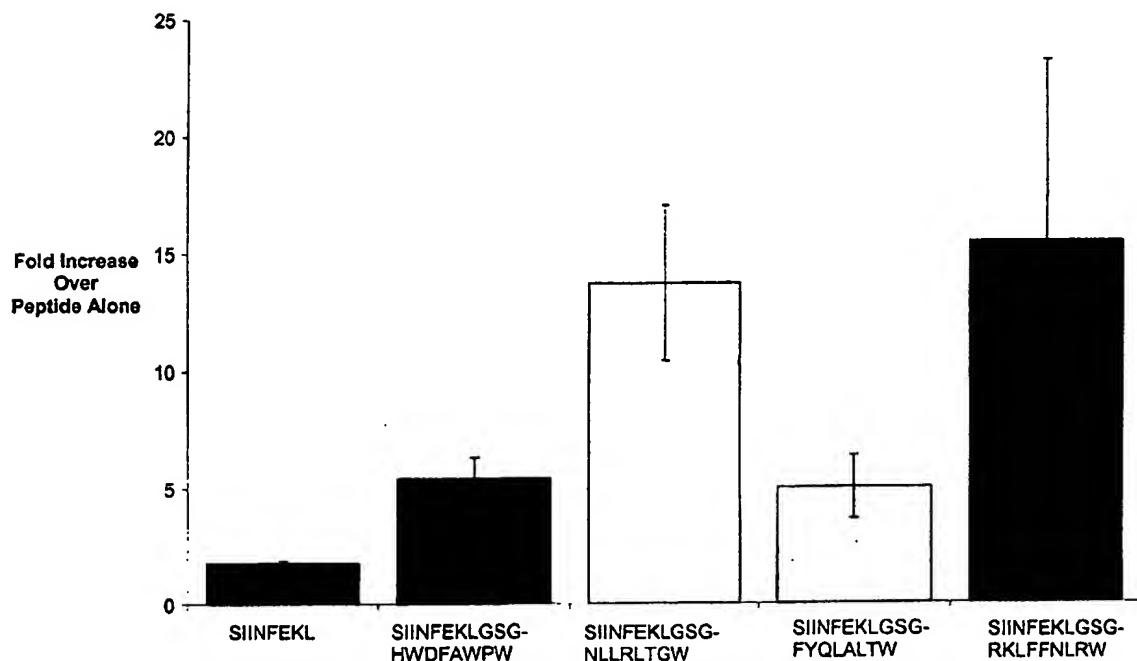


11. Using the same binding assay described in the Slusarewicz Declaration dated May 29, 2002, submitted to the instant application on October 23, 2002, the Kd of hsp70 binding to a hybrid peptide comprising the heat shock protein binding domain NLLRLTGW and the trp-2 melanoma epitope SVYDFFVWL, amino acids 180-188, was found to be 2.9 μ M. The binding of SVYDFFVWL to hsp70 has a Kd of 81 μ M.

12. Non-covalent complexes of recombinant human heat shock protein 70 and hybrid antigens were evaluated for biological activity *in vitro*. Murine peritoneal exudate cells were exposed to a complex of hsp70 and a hybrid antigen comprising OVA peptide in the presence of B3Z cells, *i.e.*, T-cell hybridomas that secrete IL-2 when presented with OVA peptide (SIINFEKL) in the context of H2-Kb. Murine peritoneal macrophages were induced by an intraperitoneal injection of thioglycollate. Five days later, mice were sacrificed and peritoneal exudate cells were recovered by peritoneal lavage. Non-adherent cells were removed and then

B3Z cells and test compounds were added. Cell-free supernatants were harvested after 18h and tested in capture ELISAs for levels of IL-2. Both hybrid antigens in complexes with hsp70 presented antigen to the OVA-specific T-cell hybridomas, the results of which are set forth in Figure 7.

Figure 7



13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Appl. No. 09/608,806
Declaration of Brian H. Barber, Ph.D.

Date: September 8, 2002

By:



Brian H. Barber, Ph.D.

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